12-12-68

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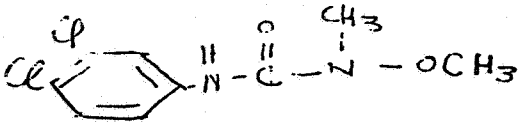
LBDale:bjc
December 12, 1968

Chemical Name	:	3-(3,4-dichlorophenyl)-1-methoxy-1-methyl-urea
Structure		
Empirical Formula	:	$C_9H_{10}Cl_2N_2O_2$
Use	:	Selective herbicide

1/14

Acute Oral Toxicity (Rat)	:	[illegible]
Subacute Oral Toxicity (Rat)	:	[illegible] mg/kg/day 13 days - No deaths but CNS depressant effects and weight gain depression.
Acute Eye Irritation (Rabbit)	:	0.1 ml 10% sol. or 10 mg dry powder faint irritation 48 hours.
Skin Irritation and Sensitization (Guinea Pig)	:	10% aqueous solution or 50% DP produced mild irritation - no sensitization.
90 Day Feeding Study (Rat)	:	80 ppm - "no effect" 320 ppm - minimal effects
2 Year Feeding Study (Rat)	:	"no effect" level - 125 ppm.
2 Year Feeding Study (Dog)	:	"no effect" level ≤ 25ppm.
3 Generation Reproduction Study (Rat)	:	[illegible] have no effect on reproductive performance or growth rates of litte[illegible]

Subacute Oral Toxicity (Rat)

Seventy albino rats were divided into 7 groups of 10 animals each (5 male, 5 female) and fed 0 (control group), 30, 60, 300, 600, 1200, and 3000 ppm lindane in their diet for 30 days. The animals were observed for mortality and signs of behavioral toxicity, weight gains and food consumption.

No growth retardation occurred in males given diets containing 60 ppm or less or in females given diets containing 600 ppm or less. Severe growth retardation was observed when diets contained 3000 ppm.

A significant increase in mortality occurred when diets containing 3000 ppm of lindane were fed.

An abnormal blood pigment, not methemoglobin, was found in the rats given the high level diet. The liver/body weight ratios were elevated in both males and females in the 3000 ppm diet and in males at the 1200 ppm level. Histological studies of the livers, kidneys and spleens were noted.

The no-effect level in males was found to be 60 ppm and in females 600 ppm.

2 Year Feeding Study (Rat)

280 albino rats were divided into 4 groups of 70 animals each (35 male, 35 female) and were maintained on diets containing 0 (control), 25, 125, and 625 ppm lindane for 2 years.

Body weights were recorded weekly during the first 3 months of the study and every 2 weeks thereafter. The clinical condition of the animals was observed daily, this included appetite, condition of coat, feces, and evidence of illness or tumor. Mortality was recorded as it occurred. Food consumption

measurements were made after 1 month and 4 months.

Periodic [illegible] samples were taken from 5 male and 5 female rats in each group pre-experimentally and at monthly intervals for the first 6 months, every 2 months for the balance of the first year, and every 3 months during the second year. A terminal blood sample was taken of all surviving rats. Observations included hemoglobin, RBC, WBC, and differential counts. Pooled urine samples were taken 3 times each year and examined for sugar and protein. Organ weights were recorded for all rats at time of autopsy. Histology was performed on selected tissues.

Growth retardation was noted only in the rats fed the 625 ppm diet, although after 48 weeks on this diet the male rats weighed as much as did the control male rats. The growth depression persisted among the female rats throughout the second year of the study.

Increased mortality was noted early in the study, particularly among the male rats fed the 625 ppm diet. Most of the deaths were attributed to respiratory infections.

Food consumption measurements indicated no interference with appetite in rats given a diet containing 625 ppm linuron.

Urine contained normal trace levels of sugar and protein.

Hematological studies conducted periodically throughout the test period gave normal values. There was no evidence of the presence of abnormal blood pigments in rats fed the 25, 125 or 625 ppm dietary levels of linuron.

Organ weights and organ weight-body weight ratios were within normal limits.

No histological evidence of tissue damage was noted in rats fed the 25 ppm and 125 ppm dietary levels of linuron. Rats fed 625 ppm dietary levels showed changes, particularly among the females, in the spleen and bone marrow that were suggestive of a hemolytic process. Five female rats fed the highest dietary level showed endometrial hyperplasia.

Reproduction studies were carried out over 3 generations involving the production of 2 litters in each generation. Performance records were comparable throughout for the rats maintained on the control diet and those fed diets containing 125 ppm linuron. The average number of pups per litter, mortality of the pups, and the average weight of pups at weaning were comparable.

The growth of the 2 litters (F_{1b}) of the F_1 generation, control and linuron fed, was comparable.

The weanling rats of the second generation (F_{2b}) fed at the 125 ppm dietary level of linuron did not grow as well as the F_{2b} control rats.

Weanling rats born in the first litters (F_{3a}) of the third generation were maintained on their respective diets (control or 125 ppm linuron) for a period of 10 weeks. The male rats fed the 125 ppm dietary level of linuron showed a slight but significant weight depression after 10 weeks on the diet.

At weaning, rats from the second litters (F_{3b}) of the third generation were sacrificed. Organ weights and organ weight-body weight ratios were comparable for the rats given the control diet and for rats fed the 125 ppm linuron diet. Histological study of tissue sections from these rats showed no evidence of any tissue change that could be attributed to the administration of linuron.

The remaininq rats were placed on their respective (control or 125 ppm linuron) diets for a period of 11 weeks. The body weights of the F_{3b} rats fed the linuron diet were,on the average, significantly greater than the control rats.

Subacute Oral Toxicity (Dog)

Two dogs were utilized in the study. One dog was fed a dose of 6 mg/kg/day linuron for a period of 30 days, the other dog was fed varying doses for the same period.

The dog fed 6 mg/kg/day showed no effect due to the chemical. The second dog showed evidence of weight loss on a daily dose of 150 mg/kg/day linuron. The same dog tolerated a dose of 60 mg/kg/day linuron for a period of 6 weeks showing only a slight weight loss.

Urine analyses were normal for most dogs. Hematological values were normal for the low dose dogs. In the high dose dogs RBC, hemoglobin values, and hematocrit percentages were slightly depressed. Organ weights were in the normal ranges for both animals. Histological studies reveal no tissue damages.

2 Year Feeding Study (Dog)

24 beagle dogs were divided into 4 groups of 6 animals each (3 male, 3 female) and administered diets containing 0 (control), 25, 125, and 625 ppm linuron for 2 years.

The dogs were housed individually and body weights were recorded weekly. The dogs were observed at regular intervals for a general clinical condition and appetite.

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Blood samples were taken pre-experimentally, after 2 weeks and every 3 months thereafter. CBC, hemoglobin, and hematocrit were recorded at each period.

Urine was collected pre-experimentally and monthly throughout the experiment and examined semiquantitatively for sugar and protein.

All dogs were sacrificed at termination and organ weights were recorded. Complete autopsies were performed and organs were prepared for histopathological study.

The body weights of the male dogs were maintained over the entire period. Slight decreases of body weight were observed in 2 dogs at the highest dietary level and 1 dog in the lowest dietary level. These changes were considered not to be related to the treatment.

One dog at the 125 ppm level was sacrificed following the appearance of paralysis in the hind quarters from factors not related to the treatment.

Urine analyses were normal..

Male dogs fed the highest dietary level showed statistically significant lower red blood cell counts, hemoglobin and hematocrit values. The values for the female dogs at this level were only slightly lower than normal. At the 125 ppm level, female dogs showed a statistically significant decrease in the RBC after 2 years on the diet whereas the values in the male dogs were within normal limits. Values for both male and female dogs at the 25 ppm dietary level were normal.

Spectral analyses of the blood showed normal oxyhemoglobin in both control and test dogs. Spectra of blood samples of all dogs at the 625 ppm level showed the presence of an abnormal pigment. Abnormal pigment was detected

in the blood of 4 of the 5 dogs examined at the 125 ppm level. Among the dogs fed the 25 ppm level, only 2 dogs showed the presence of an abnormal pigment. Blood from the control dogs showed only normal pigment.

Organ weights and organ weight-body weight ratios were within normal ranges.

Analyses for linuron residues in tissues taken from the dogs at sacrifice, showed levels that were generally proportional to the dietary content.

There was no histological evidence of tissue damage resulting from treatment in the dogs at the 25 and 125 ppm dietary levels. The dogs fed the 625 ppm level showed an arythroid hyperplasia of the bone marrow and increased accumulation of pigment in the hepatic Kupffer cells.

Reproduction Study (Rat)

Seventy-four albino rats of the Rochester strain (ex-Wistar, 1923) were divided into 2 groups of 37 animals each (15 male, 22 female) and maintained on diets containing 0 (control group) and 125 ppm linuron for a period of 14 weeks. This was the parent generation (P_0). Reproduction studies were carried out over 3 generations involving the production of 2 litters in each generation.

Twelve to sixteen females were mated in the control groups and 15-16 in the linuron-fed groups. Eleven-15 pregnancies resulted in the control groups and in the linuron-fed groups.

The largest number of pups in any group were born in the F_{3a} generation from females on the linuron diet. There was no indication of any adverse effect on linuron.

The number of pups dying in the first 5 days ranged from 2-19. There was

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no points of discrimination between the control groups and the linuron fed groups in this early mortality. No obvious differences were found in the mortalities among the control rats and the linuron fed rats.

Survival at 21 days was high. There was no indication that the ingestion of the diet containing 1-5 ppm linuron reduced growth.

There was no difference in average body weight of weanlings related to the ingestion of linuron.

Fifteen male and 15 female rats from the F_{1a} generation were maintained on the diets for a 13 week period. There was no differences in their growth performances.

Fifteen males and 22 female rats from the F_{1b} generation were maintained on the diets for a period of 12 weeks. There was no differences in their growth performances.

Eighteen male and 22 female rats of the F_{2b} generation were maintained on the diets for 12 weeks. The growth performance was the same in both the test and control groups.

Fifteen male and 15 female rats of the F_{3a} generation were maintained on the diets for a period of 13 weeks. The growth performances were better for the linuron fed than for the control rats.

Fifteen male and 15 females of the F_{3b} generation were maintained on the diets for a period of 13 weeks. The growth performances for both groups were comparable.

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CONCLUSIONS

Linuron is the accepted name for 3-(3,4-dichloro phenyl)-1-methoxy-1-methyl-urea and is used as a pre-and post-emergence herbicide in selected crops.

Linuron has an ALD of 1500 mg/kg and is only moderately irritating to the skin. Linuron is only mildly irritating to the eyes. The (no-effect) level of linurom in 2 year feeding studies was found to be 125 ppm in rats and less than 25 ppm in dogs. Linuron had no effect upon reproductive performance in a 3 generation study in rats.

The presence of an abnormal blood pigment was reported in dogs fed high levels of linuron. The pigment was not identified. Evidence of hemolysis was present in these animals. Erythroid hyperplasia of the bone marrow and increased accumulation of pigment in the liver Kupffer cells was also present.

These findings were reminiscent of findings with Diuron. In this case, at high dosage levels, hemolysis was present as was hyperplasia of the bone marrow. In the case of diuron the abnormal blood was identified as sulfhemoglobin. It is logical to assume that this is the pigment present with linuron since the compounds are very similar chemically. The conclusions reached in respect to sulfhemoglobin with diuron was that the traces of sulfhemoglobin produced should be of no greater concern than the low levels of carboxymemoglobin or methemoglobin ususally found in human blood.

Linuron poses no undue human health hazards.

AGRICULTURAL STABILIZATION AND CONSERVATION SERVICE
PESTICIDES REGULATION BRANCH
WASHINGTON, D. C. 20250

INTERDEPARTMENTAL COORDINATION OF ACTIVITIES RELATING TO PESTICIDES

Referral of Application for Registration under the Federal Insecticide, Fungicide, and Rodenticide Act

000680

1. APPLICANT
E. I. DU PONT DE NEMOURS & COMPANY
6054 DU PONT BUILDING
WILMINGTON, DELAWARE

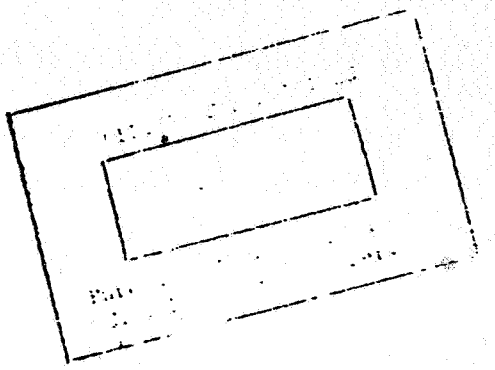
3. DATE OF REFERRAL
Jan 13, 1967

352-

2. PRODUCT
DU PONT LINUHON FLAKE TECHNICAL

4. COMMENTS BY COORDINATING AGENCY

Place the statement "Keep out of reach of children" in prominent place on the front panel



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5. BY (Name)
cls

6. DATE

7. NAME OF AGENCY

PR FORM 9 230
REVISED

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000680

PRODUCT DATA

FOR THE REGISTRATION OF A PESTICIDE

DU PONT Linuron Blake Technical

Manufactured by: E. I. du Pont de Nemours and Company (Inc.)
6054 Du Pont Building
Wilmington, Delaware

Mailing Address: E. I. du Pont de Nemours and Company
6054 Du Pont Building
Wilmington, Del. 19898

GUARANTEED ANALYSIS

Active Ingredient

Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea] ...

Inert Ingredients

. . . . . .

Supplemental Information

Manufactured at: East Chicago, Indiana

Package size generally distributed is 10 lbs.

This product is for the manufacture of [illegible]

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000680

CONFIDENTIAL

Composition

of

DU PONT Linuron Flake Technical

Product consists entirely of linuron technical - with a minimum strength of 95%.

12/24/66

DUPONT
REG. U.S. PAT. OFF.

LINURON

FLAKE

TECHNICAL

FOR THE MANUFACTURE OF WEED KILLERS ONLY

ACTIVE INGREDIENT:

Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea]	95%
INERT INGREDIENTS	5%

USDA Reg. No. [illegible]

U.S. Pat. 2,960,534

CAUTION! MAY IRRITATE EYES, NOSE, THROAT, AND SKIN.

Avoid breathing dust.
Avoid contact with skin, eyes, and clothing.
Keep from children.

NET LBS.

E. I. DU PONT DE NEMOURS & COMPANY, (INC.)
INDUSTRIAL AND BIOCHEMICALS DEPARTMENT
WILMINGTON, DELAWARE

GC 19749 0.66 Made in U.S.A. Printed in U.S.A.

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